REMARKS

The Office Action dated October 14, 2005 has been carefully considered. Claims 1, 3, 4, 10 and 36 have been amended. Claims 37 and 38 have been canceled. Claims 42-48 are allowed. Applicants respectfully point out that no rejections were presented for claims 39-41, accordingly, claims 39-41 should also be allowable. Claims 1-48 are pending. No new matter has been entered.

Amendments to claim 1 are found throughout the specification and in particular on page 4, ¶ [0016]. Amendments to claims 3 and 4 are supported by original claims 1, 3 and 4. The amendments to claim 10 are supported by original claim 10 and ¶¶ [0017] and [0216]. Amended claim 36 incorporates the limitations of original claims 37 and 38, which have been canceled.

The amendment presented for ¶ [0078] is submitted in order to correct an inadvertent error, wherein the original stated: "AI-2 is prevented from acting as a sensor for quorum sensing." The specification actually explains throughout that AI-2 is a signaling factor that pairs with a sensor. The change is not new matter and is supported by the disclosure in ¶ [0080] that the "activity" of AI-2 encompasses any aspect of AI-2's ability to act as a signaling factor in bacterial quorum sensing, growth regulation, and pathogenesis. It is also supported by the disclosure in ¶ [0007] that each system comprises a sensor-autoinducer pair; Signaling System 1 uses Sensor 1 and autoinducer-1 (AI-1), while Signaling System 2 uses Sensor 2 and autoinducer-2 (AI-2).

Double Patenting

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,559,176 to Bassler et al. Applicants respectfully traverse the rejection of claim 1.

Any obviousness-type double patenting rejection should make clear the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue would have been an obvious variation of the invention defined in a claim in the patent. *See* MPEP, Section 804. The Examiner has not stated any reasons, having merely stated the conclusion: "Clearly the patented application is an obvious variant of the present application."

(Office Action at page 3, second paragraph) "[T]he rule is that the burden of persuasion is on the PTO to show why the applicant is not entitled to a patent." *In re Epstein*, 31 USPQ2d 1817, 1825 (Fed. Cir. 1994). Since the Patent Office has not met its burden of setting forth reasons why the patent is an obvious variant of the claimed invention, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claim 10 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,936,435 to Bassler et al. The Examiner states that the patented application recites the same two steps as the present application. Applicants respectfully disagree, while conceding that the original wording lacked clarity. Applicants have amended claim 10 so that the limitations are presented in a more distinct and clearer form, so that the differences in the methods are readily distinguishable. The method of the patented invention contacts the bacterial cell with a *mixture* of the autoinducer and the compound while the method of the present invention contacts the bacterial cell only with the autoinducer analog. Thus the methods contain different steps. Applicants respectfully submit that the claims are not obvious-type double patenting and request that the rejection be reconsidered and withdrawn.

35 U.S.C. § 112, First Paragraph

Claims 1-9 and 36-38 and claims 27-35 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enabling disclosure. Applicants respectfully traverse the rejections.

The Examiner rejected claims 1-9 and 36-38 under 35 U.S.C. § 112, first paragraph, for the reason that the specification, while being enabling for the autoinducer-2 (4-hydroxy-5-methyl-2H-furan-3-one) does not reasonably provide enablement for other autoinducers-2. Claim 36 has been amended to incorporate the limitations of claims 37 and 38, and the latter two claims have been canceled. Given the Examiner's concession that the specification is enabling for 4-hydroxy-5-methyl-2H-furan-3-one, the rejection of claims 2 and 36 should be withdrawn because these claims contain limitations specifically directed to this substance.

The specification enables all of claims 1-9, as well. Claims 1-9 are directed to a method for identifying a compound that regulates the activity of autoinducer-2 which comprises, *inter alia*, contacting autoinducer-2 with the compound. The Examiner stated that the working

example is limited to contacting autoinducer-2 (4-hydroxy-5-methyl-2H-furan-3-one) with a compound that regulates the activity of autoinducer-2 and detecting an autoinducer-associated bacterial biomarker. Applicants respectfully disagree. The specification provides much more guidance and many more working examples that enable the skilled artisan to make and use the invention.

As to the method of claim 1, guidance is provided, for example, in the discussion at Example 11 (¶¶ [0306]-[0322]). Specifically, at ¶ [0310] the specification discloses that an autoinducer-2 molecule can interact with proteins to form an AI-2-LuxP-LuxQ complex that promotes both luminescence and activation of biochemical pathways for bacterial pathogenicity. The specification discloses that AI-2-LuxP-LuxQ interactions can be regulated by using an AI-2 analogue, such as pentenomycin, that can compete with endogenous AI-2 for these binding proteins. Thus, the guidance that is provided is inclusive of all the forms of AI-2 that the various bacteria produce endogenously, for example, twenty-two disclosed species of bacteria produce AI-2. *See* ¶¶ [0009] and [0314].

With regard to working examples, Figs. 16-18 present working example data on AI-2 analogs capable of inhibiting luminescence in *V. harveyi* strain BB170. Thus Figs. 16-18 show inhibition of activity of the endogenous *V. harveyi* AI-2 by these compounds. Fig. 22 presents data from a working example showing inhibition by the compound QXP031 in a CAMP assay in the bacteria *S. pyogenes*. This is a method of measuring inhibition of endogenously produced AI-2 from *S. pyogenes*. Example 12 ¶¶ [0323]-[0326] provides a working example of biofilm formation by *V. harveyi* in the presence of endogenous AI-2 as compared to biofilm formation when the exogenous compound, 4-hydroxy-5-methyl-2H-furan-3-one, was added to the media. Furthermore, biofilm formation for yet another species, *Pseudomonas aeruginosa*, is shown (Fig. 27 and ¶ [0326]) both in the presence and absence of 4-hydroxy-5-methyl-2H-furan-3-one in the media. Thus the specification has provided numerous examples of exogenously supplied 4-hydroxy-5-methyl-2H-furan-3-one, and of the effect that compounds added to the media have on the activity of endogenous AI-2 in various bacteria.

The Examiner has stated that the present invention is unpredictable unless experimentation is shown for other autoinducers-2 when contacted with a compound. Since

Applicants have summarized additional experimentation, Applicants have rebutted the unpredictability issue. The Examiner has also stated that undue experimentation would be required to practice the invention since the specification failed to provide guidance as to how other autoinducers-2 are affected when contacted with a compound that regulates their activities. Again, the guidance and working examples that Applicants have summarized rebuts the reasoning that undue experimentation would be required. In light of the fact that the Examiner has pointed to a relative skill level in the art of a Ph.D. or M.D., the guidance provided would allow the skilled artisan to make and use the invention without undue experimentation.

For all these reasons, Applicants respectfully submit that claims 1-9 and 36 are supported by enabling disclosure.

The Examiner has rejected claims 27-35 under 35 U.S.C. § 112, first paragraph, for the reason that the specification, while being enabling for a bacterial cell that is the bacterial strain of the genus *Vibrio*, does not reasonably provide enablement for other bacterial cells or strains. Given the aforementioned concession that the specification is enabling for the genus *Vibrio*, Applicants respectfully submit that the rejection of claims 33-35 should be withdrawn because these claims have limitations specifically directed to bacteria of the genus *Vibrio*.

Applicants respectfully disagree with the statement that the specification does not reasonably provide enablement for bacterial cells or strains other than the genus *Vibrio*. Claims 27-35 are supported, for example by experiments using *Streptococcus pyogenes* and *Staphylococcus aureus* in the claimed method. Two experiments are described at ¶¶ [0320]-[0322], ¶ [0059] and ¶ [0060] and Figs. 22-23. In the first working example, an overlay of *S. aureus* and *S. pyogenes* was prepared and then contacted with the compound QXP031 to demonstrate inhibition of endogenous AI-2 activity with a CAMP assay. In the second working example, *S. pyogenes* was contacted with compound QXP031 to demonstrate inhibition with a proteinase assay. These examples demonstrate the use of compounds to regulate bacterial virulence by regulating the activity of AI-2 and proteins that interact with AI-2.

Furthermore, the specification provides detailed experimental guidance on methods to assay the endogenous AI-2 production system of the bacterial strains *E. coli* and *S. typhimurium* at ¶¶ [0216]-[0250]. In addition, at ¶¶ [0251]-[0254] and ¶¶ [0335]-[0336], the specification

provides guidance for contacting the bacterial strains *E. coli* and *S. typhimurium* with various fluids including osmotic shock fluids containing AI-2 activity from *S. typhimurium* LT2, *E. coli* O157, as well as osmotic shock fluid from *E. coli* DH5α, and for determining whether the fluids act through SdiA. These experiments assayed an *ftsQ1p2p-lacZ* reporter in *E. coli* and an *rck* ::MudJ fusion in *S. typhimurium*. Notwithstanding that the AI-2 quorum-sensing factor in these bacteria did not signal to SdiA, the guidance from these experiments would enable the skilled artisan to perform further experimentation to assay for AI-2 activity substituting other genes for the SdiA. Thus, the disclosure provides ample guidance to practice the invention on bacterial strains other than the genus *Vibrio*. The Examiner stated that the present invention is unpredictable unless experimentation is shown for other bacterial cells or strains and that undue experimentation would be required because the specification failed to provide guidance for other bacterial strains or cells. Since multiple examples of that guidance and multiple working examples have now been summarized, Applicants submit that the issues of unpredictability and undue experimentation have been rebutted. Applicants respectfully submit that claims 27-35 are supported by enabling disclosure.

For all these reasons, Applicants respectfully request that the rejection of claims 1-9 and 27-36 be reconsidered and withdrawn.

35 U.S.C. § 112, Second Paragraph

Claims 10-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states that claim 10 is indefinite because of the phrase "autoinducer-2 analog" which fails to describe or show what is meant by the phrase. The Examiner points out that the claims do not disclose any autoinducer-2 analogs. Applicants respectfully traverse the rejection.

It is of no moment whether the other claims are directed to any particular autoinducer-2 analog. In order to ascertain the meaning of a limitation in a claim, it is necessary to examine the specification, not the other claims. MPEP 2173.01. The meaning of the phrase "autoinducer-2 analog" is clearly spelled out at ¶ [0081]. "Autoinducer-2 analog" means any compound with at least 10% of the autoinducer-2 activity of any stereoisomer of 4-hydroxy-5-methyl-2H-furan-3-

one, and includes the naturally-occurring autoinducer-2. Since the phrase is well-defined, Applicants respectfully request that the rejection be reconsidered and withdrawn.

In view of the foregoing, Applicants submit that all pending claims are in condition for allowance and request that all claims be allowed. A prompt action on the merits is earnestly solicited. The Examiner is invited to contact the undersigned should he believe that this would expedite prosecution of this application. It is believed that no fee is required. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2165.

Respectfully submitted,

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Diane Dunn McKay
Reg. No. 34,586
Attorney for Applicant

MATHEWS, SHEPHERD, McKAY & BRUNEAU, P.A.
100 Thanet Circle, Suite 306
Princeton, NJ 08540
Tel: 609 924 8555
Fax: 609 924 3036